GLIMEPIRIDE STUDY ON TYPE-2 DIABETIC SUBJECTS

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ABSTRACT

Objective: The aim of the present study was to monitor the efficacy of glimepiride going beyond 4mg in our daily practice, since the action of glimepiride is reproducibly dose-dependent and the dose of glimepiride can be given upto 8 mg.

Patients and Methods: This was a prospective study in which 113 subjects (56 Males 57 Females) were recruited from the OPD of Baqai Institute of Diabetology and Endocrinology. The study started from 30th October 2003 and the last subject was enrolled on 31st July 2004. Subjects having a HbA1c > 8 % on maximum dose of other Oral Hypoglycemic Agents (OHA) were given glimepiride six to eight milligrams and treatment followed up. HbA1c was rechecked after three to six months and this was taken as subjects reaching endpoint of the study.

Results: The mean baseline HbA1c of the patients was 10.17%. The patients were followed and HbA1c done after an average of 5 months. The HbA1c of subjects continuing on 6 mg of glimepiride (n= 103) was 8.73% while those on 8 mg (n=10) was 8.26%. The adjusted mean difference of HbA1c from baseline to 2nd sample for 6mg was -1.44% and for 8 mg was -1.91% which was statistically significant (p value < 0.001). Thus the percentage reduction in mean HbA1c for 6 mg was 14.2% and for 8 mg was 18.8% respectively in our subjects.

Conclusion: The reduction of mean HbA1c before and after treatment in both the 6 and 8 mg groups was statistically significant over the period of the study.

KEY WORD: Glimepride 6mg, 8mg, Type-II Diabetes, HbA1c.

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INTRODUCTION

Type 2 diabetes mellitus is usually a mixed defect of insulin deficiency and resistance. Insulin resistance is greater at the level of liver, muscle and adipose tissue[1,2] and as a result of insulin deficiency – at first relative to their requirement and later an absolute deficiency.[3] The resultant hyperglycemia results in wide-spread vascular damage that is responsible for the morbidity and mortality seen in patients with type 2 diabetes. However diabetes-related complications can be delayed or prevented through achievement and maintenance of tight glycemic control.[4-7] Such control is therefore the principal objective of anti diabetic therapy.

If diet and exercise are not able to restore and maintain normal glycemic control in patients with type 2 diabetes, pharmacologic treatment is necessary to achieve near-normal blood glucose levels and glycated haemoglobin (HbA1c) values. The sulfonylureas (SUs) are oral antidiabetic agents that can be used in patients with type 2 diabetes because they stimulate the release of insulin from

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pancreatic beta-cells and have a number of extrapancreatic effects including increased insulin-mediated uptake of glucose in peripheral tissues.[8]

Glimepiride is a third generation Sulfonylureas that is used as an anti hyperglycemic agent for the oral therapy of type 2 diabetes mellitus. Its main action is the release of insulin from pancreatic beta cells. Glimepiride specifically binds to a certain membrane protein close to the potassium channel of the beta cell membrane and reduces the opening probability of this channel. The resulting depolarisation opens voltage-dependent calcium channels and leads to calcium influx into the cell. In the presence of glucose, the elevated intracellular calcium levels trigger insulin secretion.

Extrapancreatic actions have also been demonstrated for glimepiride.[9-12] The drug improves the insulin sensitivity of peripheral tissue.[11] Glimepiride also increases the number of glucose transporter molecules in the plasma membrane of peripheral muscle and adipose tissue and enhances their glucose uptake. This agent activates insulin-mediated glycogen synthesis and lipogenesis, and it inhibits hepatic gluconeogenesis. Both the increase in insulin secretion (main mechanism of action), and the improvement of glucose utilization (additional beneficial effect), are responsible for the glucose-lowering properties of this agent.

Glimepiride is rapidly and completely absorbed after oral administration[13] and is not affected by food intake. There is no evidence of accumulation in the circulation after multiple doses.[14] Glimepiride is completely metabolized by hepatic oxidative biotransformation; the hepatic cytochrome P450 2C9 isoenzyme transforms glimepiride to the cyclohexyl hydroxymethyl derivative (M1), which is further metabolized by cytosolic enzymes to the carboxyl derivative (M2).[15] After a single dose, the elimination half-life of glimepiride is 5 hours, increasing to 9 hours after multiple doses.[13] The physiological response to physical exertion, including a reduction of insulin secretion, is maintained on therapy with glimepiride.[16]

The usual starting dose of glimepiride as initial therapy is one to two mg once daily, administered with breakfast or the first main meal. Depending on the metabolic situation, the daily dose can be increased stepwise in intervals of 1 to 2 weeks, to glimepiride 3 or 4 mg once daily. The maximum recommended dose is 8 mg once daily. Insulin is usually added when the patient's glycemic control becomes unsatisfactory on 4 mg of glimepiride in daily practice.

Since the action of glimepiride is reproducibly dose-dependent and the dose of glimepiride can be given upto 8 mg the aim of the present study was to monitor the efficacy of glimepiride going beyond 4mg in our daily practice. As the main parameter of efficacy, glycated haemoglobin (HbA1c) was recorded after 3-6 months.

PATIENTS AND METHODS

This was a prospective study in which 113 subjects were recruited from the OPD of Baqai Institute of Diabetology and Endocrinology. The study started from 30th October 2003 and the last subject was enrolled in the study on 31st July 2004.

Inclusion Criteria:

- Age 30 to 70 years,
- Type 2 diabetes,
- HbA1c greater than 8%

Subjects on any of the following doses of oral hypoglycemic agents.

- Glibenclamide 15 mg
- Gliclazide 240 mg
- Glimepiride 4 mg
- Metformin 2500 mg
- Acarbose 300 mg

Exclusion Criteria:

- Impaired Renal functions (Serum Creatinine greater than 1.5 mg/dl).
- Proliferative Retinopathy.
- Unstable Cardiovascular Disease.
- Type 1 Diabetes.

This study was approved by the Institutional Review Board of the Baqai Institute of Diabetology and Endocrinology. Subjects having a HbA1c > 8 % on maximum dose of

OHA as mentioned in inclusion criteria were shifted to Glimepiride [Evopride] 6 -8 mg and the treatment followed up at the discretion of the attending clinician and individually adjusted according to the subject's glycemic control. If the FBG was < 140 mg/dl at the end of two weeks with Glimepiride the subject was continued on the same treatment. If at any time during the study the glycemic control became unsatisfactory, treatment was given by the physician at his discretion and the subject was excluded at this point from the study. HbA1c was rechecked after 3 - 6 months and this was taken as subjects reaching endpoint of the study.

Medical history and a complete physical examination was conducted before and after the treatment period. Socio – demographic, anthropometric and biochemical investigations such as HbA1c assessed by BIORAD Variant machine using a high-performance liquid chromatography method was recorded in subject's Performa.

Data was analyzed using Statistical Package for Social Sciences (version 10.0. Chicago; IL: SPSS Inc; 1996) was used to analyze the data. Descriptive statistics was computed for demographic as well as biochemical variables. Independent sample t test was used to observe gender differences between demographic and biochemical parameters. Paired sample t test was used to compare the difference in the mean HBA1c at baseline and at the end of the study.

RESULTS

A total of 113 subjects were enrolled during the 9 months. Males and females were equally represented in the sample (Males = 56, Females = 57). Obesity defined by BMI >23 kg/m^2 was present in 86% of the subjects. The baseline data of the sample according to gender differences is shown in Table-I.

Of the113 subjects enrolled in the study, 103 were shifted from 4 to 6 mg of glimepiride while 10 subjects were shifted from 4 to 8 mg of glimepiride by the attending physician according to their glycemic control. All the subjects were followed on the basis of glycemic control and further changes in drug regimens were done by physician if required.

The mean baseline HbA1c of the patients at start of study was 10.17%. The patients were followed and HbA1c done on the subsequent visits. Analysis was done on the subjects having both readings of HbA1c.

The HbA1c of subjects continuing on 6 mg of glimepiride (n= 103) was 8.73% while those on 8 mg (n=10) was 8.26%. The adjusted mean difference of HbA1c from baseline to post treatment sample for 6mg was -1.44% and for 8 mg was -1.91% which was statistically significant (p value $\leq$ 0.001). Thus the percentage reduction in mean HbA1c for 6 mg was 14.2% and for 8 mg was 18.8% respectively in our subjects. This was taken as the endpoint of our study.

DISCUSSION

This study was planned to assess the efficacy of 6 mg and 8 mg of glimepiride for the duration of around six months in subjects with type 2 diabetes mellitus. The reduction of mean HbA1c before and after treatment in both the 6 and 8 mg groups was statistically significant over the period of the study.

The difference between the baseline and post treatment HbA1c levels was statistically significant (p value $\leq$ 0.001). Other studies have also shown a HbA1c reduction of 1.8% with a daily dose of 4 mg glimepiride over a 14 week period of therapy while reduction of 1.3%-1.8% was seen in an 8 week non-interventional study that included 22,045 patients who were receiving a daily dose of 1.8 to 2.4 mg of glimepiride.[17,18] Overall, results of efficacy studies have indicated at least therapeutic equivalence between glimepiride, glibenclimide, gliclazide and glipizide. However glimepiride achieved metabolic control at the current dosage relative to other SUs (1 – 8 mg/dl) and was able to provide maximal glycemic control with once-daily dosing.[19]

The overall evaluation was based on the values of HbA1c reduction in our study which showed a statistical significant at an average duration of 5 months (P$\leq$0.01) which suggests

Table-I: Gender differences in Anthropometric and biochemical parameters of subjects.

Parameters	*Male* *Mean ± SD*	*Female* *Mean ± SD*	*P value*
Age	56.57±13.26	53.79±15.01	0.352
Body Mass Index	26.26±5.09	28.86±4.91	0.020
Creatinine	1.25±1.16	0.85±0.13	0.041
Cholesterol	180.45±34.20	197.13±31.99	0.054
Triglycerides	170.49±76.05	177.17±64.24	0.717
HDL	41.70±17.34	37.79±7.51	0.269
LDL	105.40±26.58	123.21±27.94	0.015
Systolic Blood pressure	129.95±18.94	130.49±22.07	0.907
Diastolic Blood pressure	80.33±13.19	83.44±10.74	0.247
Fasting Plasma glucose	195.76±61.73	222.56±71.48	0.124
Random Plasma glucose	271.64±52.70	294.38±76.11	0.399

the steadying of pancreatic functions with glimepiride.

Thus in conclusion we have seen that 6 mg and 8 mg of glimepiride reduces HbA1c in our subjects for the average duration of 5 months and can be used effectively. As seen in other prospective studies such as DCCT or UKPDS the glycemic control becomes poor with the passage of time and changes are required in the treatment modalities to achieve desirable HbA1c.

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